REMARKS

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on January 13, 2004, in which claims 1-16 were rejected and 17-38 were withdrawn from consideration. With this Amendment, independent claims 1, 3 and 4 are amended. As such, Applicant respectfully request reconsideration and allowance of pending claims 1-16.

The Office Action objected to the specification under MPEP § 608.01, stating:

> The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, such as on page 31, line 6 and page 32, line 13. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. (January 13, 2004 Office Action; Page 2).

With this Amendment, Applicant has amended the specification in accordance with the Examiner's instructions. As such, the hyperlink has been deleted from page 31, line 6 and from page 32, line 13. As such, the above-identified objection to the specification is overcome.

Claim Rejections under 35 USC § 112:

The Office Action rejected claims 1-3 and 5-16 under 35 U.S.C. §112, second paragraph, stating:

> In claim 1, last three lines, access to a database with sample information causes the claim to be vague and indefinite due to unclear antecedent basis as to whether the sample cited in the last line of claim 1 is required to be one of the samples cited in claim 1, line 1, or whether another sample may be meant such as a comparative sample which is not on the microarray. Clarification of this issue via clearer claim wording is requested. Claims 2, 5-9, and 11-16 are also rejected due to their direct or indirect dependency from claim 1.
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> Claim 3 recites the phrase "frozen cells or tissue" which is vague and indefinite. It is unclear if only the cells are intended to be frozen or if the tissue is also intended to be frozen. Clarification of this phrase via clearer claim wording is requested. Claims 5-16 are also rejected due to their dependency from claim 3.

With this Amendment, the Applicant has amended independent claim 1 to clarify the claim language; in addition, Applicant has amended claim 3 in order to clarify the claim language. Applicant believes that these amendments overcome the above-identified rejection of claims 1-3

and claims 5-16. As such, Applicant respectfully requests reconsideration and allowance of claims 1-3 and claims 5-16.

Claim Rejections under 35 USC § 102:

The Office Action rejected claims 1, 2, 5, 6, 10-13, and 15-16 are under 35 U.S.C. §102(e)(2) as being anticipated by U.S. Patent No. 6,553,317 to Lincoln et al. The Office Action stated:

> Lincoln et al. disclose the use of bioinformatics to study genes differentially expressed or commonly expressed in different tissues or cell lines, such as normal (normally proliferating cells) and cancerous tissue (abnormally proliferating cells) (col. 1, lines 46-48). Lincoln et al. disclose using a microarray with multiple samples (col. 3, lines 10-12). Lincoln et al. disclose processing clones in groups on a 96-well plastic culture dish with each chamber/well comprising an indentation in the dish to separate samples (col. 12, lines 20-25) which represents a stably associated samples with a distinct, known sublocation on a substrate, as stated in instant claim 1. Lincoln et al. disclose a barcode (identifier) for a lot or 96-well plate whose value is placed in a barcode field of a table in a database (col. 21, lines 30-41) which represents a substrate with an identifier that provides access to a database, as stated in instant claim 1. The samples in a plastic culture dish represent the sample (tissue or cells) being plastic-embedded, as stated in instant claim 10. The information on the plastic culture dish, including precise sample location with lot and well information, is recorded for each sample and given to customers (col. 12, lines 29-36). Lincoln et al. disclose using a relational database system for storing biomolecular sequence information with biological annotations (col. 2, lines 14-20) including information identifying (identifiers) sequences (col. 2, lines 28-34). Lincoln et al. disclose a system allowing a user to selectively view information regarding sequences and reagent specifications (col. 2, lines 34-37) including a graphical user interface where a query is entered and matches between query and information is displayed (col. 2, lines 46-50). Lincoln et al. disclose using a relational database with tables (col. 15, lines 44-49) including a library table that includes records of each library in the gene expression database including an identifier (LibraryID) (col. 16, lines 7-9). Lincoln et al. disclose the library table as having a "TissueID" attribute that is inherited from a "TissueSpecimen" table) and a "Tissue_Category" attribute as well as a "Lib_Description" attribute including information such as tissue name, disease state, patient age/gender (col. 16, lines 6-32). Lincoln et al. disclose providing further information about a donor in a "MedicalHistory" table including information such as a problem such as breast cancer, breast, and neoplasm (col. 20, lines 33-40), as stated in instant claim 6. Lincoln et al. disclose using a network to which the network server and clients are connected (col. 13, lines 3-9). Lincoln et al. disclose entries in various results screens may provide links to other information in the database (col. 23,

> lines 10-13) as stated in instant claim 2. Lincoln et al. disclose each tissue specimen (as uniquely identified by TissueID) may have several diagnoses (i.e. normal, diseased, involved, cancerous) and each donor may provide multiple tissue specimens (col. 19, lines 35-67). This act of providing multiple tissue specimens that are "cancerous" or "involved" is reasonably interpreted to include specimens from sites of a secondary metastasis of cancer, as stated in instant claim 16. Lincoln et al. disclose different development stages (col. 20, lines 13-14) as stated in claim 11. Lincoln et al. disclose studying or monitoring drug resistance in certain tissue (col. 5, lines 1-3) which represents substantially homogeneous cells (as stated in instant claim 13) and samples from patients treated with a drug (as stated in instant claim 15)(January 13, 2004 Office Action; Pages 4-5).

With this Amendment, Applicant has amended independent claims 1, 3 and 4 to require the limitation that **each sample of the microarray exhibits a biological characteristic representative of a stage of cancer**. The Applicant's claimed invention is an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**. As such, the oncology microarray of the present invention allows for the simultaneous comparison of a biological characteristic of a large number of cell and/or tissue samples wherein the samples may represent various cells and/or tissues at various stages of cancer. The Applicant's claimed invention allows for the comparison of a pateint's tissue and/or cell sample with the samples of the microarray to determine the progression of the patient's illness. Applicant believes that the amendments to independent claims 1, 3 and 4 clearly distinguish the Applicant's claimed invention over the Lincoln et al. disclosure. As such, Applicants respectfully requests reconsideration and allowance of claims 1, 2, 5, 6, 10-13, and 15-16.

To anticipate a claim, the reference must teach every element of the claim. M.P.E.P. 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. 2131. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. 2131.

Lincoln et al. does NOT disclose a microarray. Lincoln et al. discloses **a relational database system** for storing biomolecular sequence information together with biological annotations detailing the source of the sequence information, and associated reagent information.

Lincoln et al mentions the phrase "microarray" in two passages of the specification. Both are merely general references to the use of a "biological microarray." First, the Lincoln et al. reference states:

> **The present invention further provides a reagent clone** identified by a process, at least partially implemented on a computer system, for establishing a set of reagent clones. The process involves **grouping initial sequences of polynucleotide inserts in a plurality of clones into a master cluster, assembling the initial sequences of the master cluster into one or more contiguous sequences, such that relationships of sequences to each other in the master cluster are elucidated,** and nominating at least one clone represented by a master cluster as a reagent clone, according to specified priority criteria. **A set of reagent clones may also be nominated according to such a method. The set of reagent clones may have a variety of uses including as hybridizable elements on a biological microarray.** (Lincoln et al; Col. 2, Line 66-Col. 3, Line 12)(Emphasis added).

As stated in the cited passage, Lincoln et al. discloses a reagent clone and a method of generating (sequencing) the reagent clone. Once the reagent clone has been produced by the Lincoln et al. process it then has a variety of uses, i.e. **as hybridizable elements on a biological microarray.** As such, the cited passage clearly does NOT anticipate a oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**. The passage merely discloses that the product of the Lincoln et al process may be used in conjunction with microarrays. The Applicant does not believe that such a general reference to a microarray anticipates the claimed invention.

Second, Lincoln et al. discloses:

> As noted above, in one aspect, **the invention provides a set of reagents.** As used herein, a reagent is a clone which has been selected from a library or libraries of clones based on criteria designed to identify clones which are good candidates for further research. A reagent clone has been resequenced and verified so that, for example, it may be provided to third parties for further research. **A reagent may be used, for example, to do additional sequencing on the clone**

> **insert; the clone may be placed in an expression vector to make its associated protein; the clone's expression may be monitored, for example, using a biological microarray or northern blot technique; the reagent may be used to identify (pull out) additional related clones; or a set of reagent clones may be used as hybridizable elements on a biological microarray...** (Lincoln et al, Col. 8, Line 57-Col. 9, Line 4)(Emphasis added).

The above passage recites that the Lincoln et al invention, **the set of reagents**, may be monitored using a biological microarray; in addition, Lincoln et al states that **"a set of reagent clones may be used as hybridizable elements on a biological microarray"**. As such, the cited passage clearly does NOT anticipate an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**.

In summary, it is clear that Lincoln et al. is NOT disclosing an oncology microarray of the present invention. Lincoln et al. discloses a relational database system which may be used in obtaining sequence information. Applicant has searched the Lincoln et al. reference and cited the only two passages of the cited reference which refer to microarrays; both of the above cited passages merely make a general reference to the use of the Lincoln et al. invention, the set of reagents, with a biological microarray.

Contrary to the Lincoln et al. reference, the instant application discloses an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**.

Claim Rejections Under 35 USC § 103:

The Office Action rejected claims 1-16 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,553,317 to Lincoln et al. in view of Schraml et al. (Clinical Cancer Research, August 1999, vol. 5, pages 1966-1975) and Lehman et al. (Cancer Research, February 2000, vol. 60, pages 1062-1069). The Office Action stated:

> Lincoln et al. describe the use of bioinformatics to study genes differentially expressed or commonly expressed in different tissues or cell lines, such as normal (normally proliferating cells) and cancerous tissue (abnormally proliferating cells) (col. 1, lines 46-48). Lincoln et al. describe using a microarray with multiple samples (col. 3, lines 10-12). Lincoln et al. describe processing clones in groups on a 96-well plastic culture dish with each chamber/well

comprising an indentation in the dish to separate samples (col. 12, lines 20-25) which represents a stably associated samples with a distinct, known sublocation on a substrate, as stated in instant claim 1. Lincoln et al. describe a barcode (identifier) for a lot or 96-well plate whose value is placed in a barcode field of a table in a database (col. 21, lines 30-41) which represents a substrate with an identifier that provides access to a database, as stated in instant claim 1. The samples in a plastic culture dish represent the sample (tissue or cells) being plastic-embedded, as stated in instant claim 10. The information on the plastic culture dish, including precise sample location with lot and well information, is recorded for each sample and given to customers (col. 12, lines 29-36). Lincoln et al. describe using a relational database system for storing bimolecular sequence information with biological annotations (col. 2, lines 14-20) including information identifying (identifiers) sequences (col. 2, lines 28-34). Lincoln et al. describe a system allowing a user to selectively view information regarding sequences and reagent specifications (col. 2, lines 34-37) including a graphical user interface where a query is entered and matches between query and information is displayed (col. 2, lines 46-50). Lincoln et al. describe using a relational database with tables (col. 15, lines 44-49) including a library table that includes records of each library in the gene expression, database including an identifier (LibraryID) (col. 16, lines 7-9). Lincoln et al. describe the library table as having a "TissueID" attribute that is inherited from a "TissueSpecimen" table) and a "Tissue_Category" attribute as well as a "Lib_Description" attribute including information such as tissue name, disease state, patient age/gender (col. 16, lines 6-32). Lincoln et al. describe providing further information about a donor in a "MedicalHistory" table including information such as a problem such as breast cancer, breast, and neoplasm (col. 20, lines 33-40), as stated in instant claim 6. Lincoln et al. describe using a network to which the network server and clients are connected (col. 13, lines 3-9). Lincoln et al. describe entries in various results screens may provide links to other information in the database (col. 23, lines 10-13) as stated in instant claim 2. Lincoln et al. describe each tissue specimen (as uniquely identified by TissueID) may have several diagnoses (i.e. normal, diseased, involved, cancerous) and each donor may provide multiple tissue specimens (col. 19, lines 35-67). This act of providing multiple tissue specimens that are "cancerous" or "involved" is reasonably interpreted to include specimens from sites of a secondary metastasis of cancer, as stated in instant claim 16. Lincoln et al. describe different development stages (col. 20, lines 13-14) as stated in claim 11. Lincoln et al. describe studying or monitoring drug resistance in certain tissue (col. 5, lines 1-3) which represents substantially homogeneous cells (as stated in instant claim 13) and samples from patients treated with a drug (as stated in instant claim 15). However, Lincoln et al. do not describe using frozen cells or tissue, bodily fluid, 10% samples from different tissues, five different tumor types, samples greater than about 0.6 mm in diameter, and cancer-specific markers.

Schraml et al. describe using tissue microarrays for gene amplification surveys in many different tissue types (title). Schraml et al. describe using a tissue microarray consisting of samples from 17 different tumor types with 397

individual tumors arrayed in a single paraffin block (representing at least about 10% of the samples of the microarray, as stated in instant claim 7) using minute tissue samples (diameter, 0.6 mm) (abstract and Figure 1) which is greater than about 0.6 mm in diameter, as stated in instant claims 7, 8, and 9. Schraml et al. describe finding gene markers (i.e. CCND1) amplified in breast and other cancerous tissue types (abstract and page 1966, col. 2, first paragraph), as stated in instant claims 6 and 14. Schraml et al. describe hundreds of samples are precisely arrayed in a new paraffin block (page 1966, col. 2, second paragraph) which represents stably associated samples with distinct, known sublocations on a substrate, as stated in instant claims 1 and 4. Schraml et al. describe the precise positioning of tissue specimens to enable the generation of multiple replicate array blocks, each having samples from the same tissue specimens at identical coordinates (page 1970, col. 2), as stated in instant claims 1 and 4. Schraml et al. describe using frozen tissue samples from primary tumors (abnormally proliferating cells) and normal tissues (normally proliferating cells) and embedding the specimens in paraffin (page 1966, col. 2, third paragraph), as stated in instant claims 3, 5, and 10. Schraml et al. describe using tumors in different stages and grades, including 96 breast tumors (page 1967, col. 1, second paragraph), as stated in instant claims 11 and 12.

Lehman et al. describe studying breast cancer patients for activity of exon and intron base changes in the p53 gene (abstract). Lehman et al. describe patient information, such as age (abstract). Lehman et al. describe gene studies in response to drug treatment (abstract). In Table 1, Lehman et al. describe various statistics of patients including the stage of breast cancer. Lehman et al. describe coding the samples from patients and entering the information into a database (page 1063, col. 1, first paragraph). Lehman et al. describe collecting blood (bodily fluid) from breast cancer patients for analyses (page 1063, col. 1, first paragraph), as stated in instant claim 4. Lehman et al. describe using paraffin-embedded tumor specimens and samples from patients undergoing drug treatments (page 1068, col. 1, third paragraph), as stated in instant claims 10 and 15.

Lehman et al. state the identification of woman at risk for development of breast cancer will have important implications for the prevention of cancers, treatment strategies, and improved cure rates of these patients (page 1062, col. 2, third paragraph). Schraml et al. state their tissue microarray technology has the potential to greatly facilitate analysis of alterations in multiple tissue types (page 1966, col. 2, second paragraph). Schraml et al. state that tumor arrays are a powerful tool to rapidly screen different tumor types for gene copy number alterations (page 1966, col. 2, second paragraph). Schraml et al. state they have demonstrated the power of using minute arrayed tissue specimens for tumor screening (abstract). Lincoln et al. state bioinformatics includes methods to search databases quickly to analyze information and make predictions (col. 1, lines 31-37). Lincoln et al. state information manipulation has been made easier to perform and understand with the development of sophisticated computer

> database systems (col. 1, lines 62-64). It would have been obvious to one of ordinary skill in the art at the time the invention was made to make improvements to existing gene expression techniques tied to relational database systems, as stated by Lincoln et al., because even though these systems provide great power and flexibility in analyzing gene expression information, this technology is still in its infancy and further improvements are required to accelerate biological research for numerous applications (Lincoln et al. col. 2, lines 6-12). Therefore, it would have been obvious to one of ordinary skill in the art to improve efficiency of microarray analyses with minute frozen and bodily fluid samples from multiple cancer patients and multiple tumor types (as stated by Schraml et al. and Lehman et al.) and relaying such information of relational database systems (as stated by Lincoln et al.) in order to accelerate research and evaluation in therapeutic pharmaceutical development and other fields by providing broad amounts of important information to clients in an easy to perform and understand format, as stated by Lincoln et al. (col. 1, line 62 to col. 2, line 28).
>
> Thus, Lincoln et al., in view of Schraml et al. and Lehman et al., motivate the instant claims. (January 13, 2004 Office Action; Pages 6-10).

As discussed above, the Applicant has amended independent claims 1, 3 and 4 to further differentiate the Applicant's claimed invention from the Lincoln et al. disclosure. Further, neither the Schraml et al. reference nor the Lehman et al reference cure the deficiency of the Lincoln et al. reference. As such, applicants believe that the above-identified amendment overcomes the present §103(a). Applicant respectfully requests reconsideration and allowance of claims 1-16.

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. 2143.01. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). See also *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); M.P.E.P. 2143.01.

Lehman et al. discloses:

> ...We now provide evidence that the p53 13964 base is mutated in patients who have familial breast carcinoma but not sporadic breast cancer. Furthermore, this

> mutation inhibits apoptosis and prolongs cell survival following DNA damage and thus may indeed affect breast cancer risk. The identification of women at risk for the development of breast cancer will have important implications for the prevention of cancers, treatment strategies, and improved cure rates of these patients. (Lehman et al., page 1062).

In discussing microarrays, Lehman et al. discloses:

> **Immunohistochemistry for Somatic p53 Mutations.** Following identification of the patients with the p53 intron 6 13964^{GC} base change, the individual 10% formalin-fixed and paraffin-embedded blocks were processed for immunohistochemical staining as described previously (26). After blocking 5-μm sections with goat suppressor serum, p53 protein levels were determined by using the DO1 monoclonal antibody (Oncogene Science, Uniondale, NY) to mutant p53 protein at a 1:1000 dilution. Positive staining was defined by nuclear staining only within the invasive breast cancer component...(Lehman et al, Page 1063).

As such, Lehman et al. does disclose the use of a microarray to analyze samples; however, Lehman et al. does NOT disclose an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**.

Lehman et al. discloses the identification of a mutation in a sequence and correlates the data to determine a relationship between the mutation and breast cancer. The use of a microarray allows for multiple samples to be analyzed simultaneously.

Contrary to Lehman et al, the Applicant's claimed invention comprises an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**. Comparing a patient's cell and/or tissue sample with the various samples on the microarray allows for the determination of the progression of a patient's illness.

As such, the Lehman et al. reference does NOT cure the deficiencies of the Lincoln et al. reference. Therefore, Applicant respectfully requests reconsideration and allowance of pending claims 1-16.

Similar to our analysis of the Lehman et al. reference, Schraml et al. discloses the use of a tissue microarray but does NOT disclose an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**.

Schraml et al. discloses:

> Gene amplification are common in many different tumor types and may confer diagnostic, prognostic, or therapeutic information for patient management. Tedious experiments are often required to determine which tumor types have amplifications of a specific oncogene. To facilitate rapid screening for molecular alterations in many different malignancies, a tissue microarray consisting of samples from 17 different tumor types was generated. (Schraml et al., Abstract).

Like Lehman et al., Schraml et al. discloses a microarray for simultaneous analysis of gene amplification of a large numbers of samples; however, Schraml et al. does NOT disclose an oncology microarray comprising various cell and/or tissue samples wherein the various cell and/or tissue samples **each exhibit a biological characteristic representative of a stage of cancer**. As such, Schraml et al. does not cure the deficiencies of Lincoln et al. and/or Lehman et al. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1-16.

In summary, the cited prior art references, alone or in combination, do no anticipate, suggest or make obvious Applicant's claimed invention in pending claims 1-16 and the rejections in the Office Action should accordingly be withdrawn. Reconsideration and allowance of pending claims 1-16 is respectfully requested.

With this Amendment, Applicants have made an earnest effort to respond to all issues raised in the Office Action of January 13, 2004, and to place all claims in condition for allowance. No amendment was made for the purpose of narrowing the scope of any claim, unless Applicants have argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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